Remarks

Claims 221-225, 232-239, 242-245, 247, 249, 251-253 and 255-262 are currently pending in the application. Claims 221, 224, 232, 237, 244, 249 and 252 are amended in order to more clearly define the invention , as discussed individually below. Claims 255-262 are added, and include product by process type claims as discussed in the August 2004 interview. The amendments find support in the specification and are discussed in the relevant sections below.

Interview

Applicants appreciate having had the opportunity to discuss this application with Examiner Lacourciere on August 3, 2004. Proposed draft amendments to the claims were presented as a point of discussion. The Examiner agreed that the language of these proposed claims, which has been incorporated into the newly amended claims above, appeared sufficient to overcome the outstanding 112 second paragraph rejections. Also discussed were the new matter rejections and product by process claims. New claims have been added which encompass product by process limitations.

Objection to the Specification under 35 U.S.C. 112

The Examiner contends that no support could be found for the aspects of the invention described in the summary of invention which was newly added 4-23-03, specifically "wherein the oligoribonucleotides comprise a 3'-overhang, including a single base overhang".

Applicants traverse the objection on the grounds that Examples 1 and 2 of the specification as originally filed provide support for oligoribonucleotides that comprise a 3'-overhang, as described in the Remarks section that accompanied the summary of

invention which was newly added 4-23-03. This traversal is further developed in the response to the outstanding new matter rejection below.

Claim Rejections – 35 USC 112

Claims 221-225, 236-239, 241-245, 247 and 249-252 are rejected under 35 USC 112, Second Paragraph

The Examiner contends that Claims 221 and dependent claims are indefinite because it is unclear what structure is being claimed. The Examiner asks for clarification of the elements of the claimed oligoribonucleotide, and questions how a dsRNA can be self-complementary and also be complementary to an RNA transcript. Similarly the Examiner contends Claim 252 is indefinite because it recites a double stranded structure fully complementary to an RNA transcript, and because it is unclear what structure is being claimed.

In order to more clearly define the claimed invention, the elements of newly amended claims 221 and 252 are:

- an isolated oligoribonucleotide consisting of two separate complementary strands (dsRNA) and a 3' overhang,
- the dsRNA is not more than 49 nucleotides in length,
- one strand of the dsRNA is complementary to less than the full length of an RNA transcript of a mammalian target gene.

The Examiner contends Claim 224 and its dependent claims are indefinite because "it is unclear how the double stranded structure can consist of two strands but then comprise another element (comprises a linker)".

In order to more clearly define the claimed invention, Claim 224 has been newly amended to recite (in part) "...an isolated oligoribonucleotide consisting of two RNA

strands which are fully complementary to each other (dsRNA), a linker between the two RNA strands, and a 3' overhang ..."

The Examiner contends Claim 237 and its dependent claims are indefinite because "it is unclear how the double stranded structure can consist of two strands but then comprise another element (comprises a linker)".

In order to more clearly define the claimed invention, Claim 237 has been newly amended to recite (in part) "...an isolated oligoribonucleotide consisting of two complementary strands (dsRNA), a 3' overhang and a linker, ..."

The Examiner contends that Claim 249 is indefinite because "it is unclear how a double stranded structure (which requires two self-complementary strands) can be fully complementary to an RNA transcript (which is single stranded)".

In order to more clearly define the claimed invention, Claim 249 has been newly amended to recite (in part) "...wherein one strand of said double-stranded structure is fully complementary to less than the full length of an RNA transcript of a mammalian target gene".., and claim 221 from which claim 249 depends has been amended to recite (in part) "....wherein one strand of the dsRNA is complementary to less than the full length of an RNA transcript of a mammalian target gene...".

In view of the claim amendments designed to more fully define the recited oligoribonucleotide, Applicants respectfully request reconsideration and withdrawal of these 112 second paragraph rejections.

New Matter Rejection

Claims 221-225, 232-239, 241-245, 247-254 are rejected under 35 USC 112, First Paragraph.

I Inherency of a double stranded RNA structure comprising a 3' overhang disclosed in the specification.

The Examiner contends that the dsRNA in Example 1 does not appear to result in a product that the skilled artisan would recognize as having a single base 3' overhang. Specifically the examiner asks "why in a complete digestion of the RNA, the bond between the UC at each end would not be cleaved" since the "RNAses used include RNAse A, which cleaves after C's and U's .."

However, the dsRNA described in Example 1 does result in a product that the skilled artisan would recognize as having a single base 3' overhang because it was generated by RNAse A which cleaves 3' of single-stranded C and U ribonucleotides.

At each end of the annealed transcripts, the C ribonucleotide is the last (most 3') ribonucleotide of the double stranded region, and the U ribonucleotide, which is immediately 3' to the C residue, see below, is the first ribonucleotide of the single stranded region. Accordingly cleavage will occur only after (i.e. 3' of) the single stranded U ribonucleotide, but not between the double stranded C residue and the single stranded U residue. Cleavage by RNAse A cannot occur after (i.e. 3' of) the double stranded C residue, since RNAse A cleaves only at the 3' side of a single stranded C or U residue.

II Support for the Broad Scope of Oligonucleotides Now Being Claimed

The Examiner contends that the "inherent characteristic present in this ***one example*** in the specification, ...does not provide support for the broad scope of oligonucleotides now being claimed" (emphasis added).

However, the specification has exemplified ***more than one example*** of a dsRNA having a 3' overhang, and directs attention to Example 2, wherein another dsRNA comprising a transcript with a ***different sequence*** is noted.

Example 2 illustrates the production of a dsRNA with a 3' overhang that has a ***different sequence***, using the same method as shown in Example 1. The dsRNA with a 3' overhang of Example 1 is directed to a transcript from a CMV gene, the dsRNA of Example 2 is directed to a transcript from a GFP gene.

The Examiner contends that "dsRNAs of a ***different sequence*** would not result in a similar overhang even if made using a ***similar method***" (emphasis added).

However, one of skill would recognize that by following the method steps of examples 1 and 2, the generation of the 3'overhang is not dependent on the sequence of the transcript of interest, but is a result of the sequence of the promoters flanking the transcript of interest in the vector, and a result of linearizing the vector at restriction enzyme recognition sites that flank both promoter regions.

As described in Figure 1 of the instant application, DNA encoding the transcript of interest is inserted between a T7 promoter and an SP6 promoter in a circular plasmid vector. Transcripts under the control of the T7 promoter have, at their 3'end, a sequence complementary to the SP6 promoter, because the vector was linearized at a restriction site (Bam H1) outside the SP6 promoter. Similarly, transcripts under the control of the SP6 promoter have, at their 3'end, a sequence complementary to the T7 promoter, because the plasmid was linearized at a restriction site (Eco R1) outside the T7 promoter.

Upon hybridization of the transcripts generated by the T7 promoter with the transcripts generated by the SP6 promoter, a double stranded oligoribonucleotide is formed which has a single stranded flanking region extending from the 3' ends of each RNA transcript. This single stranded region extending from the 3' ends of each RNA transcript contains a sequence complementary to the region of the T7 or SP6 promoter which is immediately 5' to the transcription initiation site of the promoter. The first nucleotide of the single stranded region correlates to the first nucleotide immediately upstream of the transcription initiation site. In the case of both the T7 and SP6 promoter this nucleotide is T. See Appendix 1 for sequences of T7, SP6 and T3 promoters.

Using the RNAse digestion of hybridized transcripts generated using linearized vectors encoding the transcript of interest between a T7 and a SP6 promoter as described in Examples 1 and 2, the first ribonucleotide of the 3' single stranded flanking regions immediately adjacent to the double stranded region is always a "U". This "U" is always present regardless of the dsRNA sequence of interest. This "U" represents the complement of the first nucleotide immediately 5' to the transcription initiation site of

both the T7 promoter and the SP6 promoter. The 3' overhang is generated by a complete digestion of the single stranded region with RNAses A and T1 which cleaves at the 3' side of single stranded U, G and C. Specifically, since RNAse A cleaves at the 3' side (as opposed to the 5' side) of single stranded Us, the single stranded U immediately adjacent to the 3' side of the double stranded region is left as the single nucleotide overhang of the dsRNA.

Again, the U corresponds to the reverse complement of the nucleotide (A) adjacent to the tanscriptional start site of both the SP6 and T7 promoter sequences and explains why there is the same single 3' overhang on both strands.

III The Application inherently supports the Written Description Requirements for a claimed genus of dsRNAs with a 3' overhang.

The Examiner asserts that the "inherent characteristics present in this one example in the specification...does not provide support for the broad scope of oligonucleotides now being claimed".

Applicants note that "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

The 3' overhang is necessarily present in the dsRNA produced by the method steps detailed in Example 1 and Example 2 of the specification. The CMV dsRNA with the inherent 3' overhang in Example 1. Similarly, the YFP dsRNA described in Example 2 also has an inherent 3' overhang, being generated with the same method steps used to generate the CMVdsRNA of Example 1. The presence of a 3' overhang in both the CMV dsRNA of Example 1 and the YFP of Example 2 would be so recognized by persons of ordinary skill in molecular biology. The MPEP states that missing descriptive matter can

be inherent if the missing descriptive matter is necessarily present in the referenced disclosure, and if enables persons of ordinary skill to recognize that the missing descriptive matter is necessarily present.

The MPEP also states that inherent features may later be amended in the application without introducing prohibited new matter. *In re Reynolds*, 443 F.2d 384, MPEP 2163.07(a). MPEP 2163.07(a)states that "By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973)."

Applicants further contend that the instant disclosure supports the Written Description Requirements for a claimed genus of dsRNAs with a 3' overhang as set forth in *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406:

i. sufficient description of a representative number of species by actual reduction to practice
ii. disclosure of relevant, identifying characteristics,
iii. a combination of such identifying characteristics,

The instant disclosure (in particular the Examples section) demonstrates possession of the claimed invention through reduction to practice of the claimed invention. Reduction to Practice is best means to show possession, *Cooper v. Goldfarb*, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998). See also *UMC Elecs. Co. v. United States*, 816 F.2d 647, 652, 2 USPQ2d 1465, 1468 (Fed. Cir. 1987).The generation of multiple dsRNAs with a 3' overhang as exemplified in Examples 1 and 2 show Reduction to Practice of a genus of dsRNAs with a 3' overhang.

Further, the disclosed Figures illustrating structure of Vector used for producing dsRNA of any sequence of interest show possession of the claimed invention of a dsRNA

with a 3' overhang. The MPEP says that possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art. See *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966 ("written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention"). Figure 1 of the instant disclosure illustrates a vector diagram with restriction sites for inserting the gene fragment of interest and locations of in vitro transcription promoters flanking the gene fragment of interest. The use of this vector in methods to generate dsRNAs with inherent 3' overhangs is disclosed throughout the specification, particularly in the Examples Section, and demonstrates possession of dsRNAs with inherent 3' overhangs by Applicant at the time of filing.

The Examiner asserts that "the inherent characteristic present in this one example in the specification, wherein this characteristic was not even appreciated or pointed out by the invention at the time of the invention, does not provide support for the broad scope of oligoribonucleotides now being claimed".

Applicant note that Reduction to Practice is proof of conception as detailed in Spero v. Ringold and Rosenkranz,CITATION. "Since the conception of an invention is a mental act, known only to its originator, it follows that it must be proven by evidence showing what the inventor has disclosed to others and what the disclosure means to one of ordinary skill in the art. In this light the standard for proving conception is not essentially different from that required for proving reduction to practice or adequacy of support in a disclosure for a claim. In all these cases the proof of disclosure by the

inventor must be interpreted in light of what it means to a person of ordinary skill in the art." Applicant contends that a person of ordinary skill in the art would recognize that the instant disclosure discloses multiple dsRNAs each of which have a 3' overhang.

Finally, Applicants contend that the PTO has not met its burden of demonstrating lack of written description. There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims"). For the reasons elaborated in the preceding paragraphs, Applicants contend that the PTO has not presented sufficient evidence or reasons why persons skilled in the art would not recognize in the instant disclosure a description of a genus of dsRNAs with a 3' overhang as defined by the claims. Therefore Applicants respectfully request reconsideration and withdrawal of the new matter rejection and the accompanying objection to the specification based on putative new matter.

Conclusion

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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